Vegetarian or gluten-free diets in patients with inflammatory bowel disease are associated with lower psychological well-being and a different gut microbiota, but no beneficial effects on the course of the disease

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Abstract: Background Many inflammatory bowel disease (IBD) patients follow a restrictive diet due to perceived positive effects on their symptoms. We assessed the prevalence of vegetarian (VD) and gluten-free diets (GFDs) in IBD patients, the reasons for following such a diet, and whether nutrition has an impact on disease activity and microbiota composition. Methods We included 1254 patients from the Swiss Inflammatory Bowel Disease Cohort Study with prospective acquisition of clinical data and psychosocial, disease-related and lifestyle factors between 2006 and 2015. Dietary habits were assessed through a self-report questionnaire. In 92 patients, we analysed intestinal mucosa-associated microbial composition using high-throughput sequencing. Results Overall, 4.1% (= 52) of the patients reported following a VD and 4.7% (= 54) a GFD. No differences regarding disease activity, fistula, hospitalization or surgery rates were observed. Patients on a VD or GFD had significantly higher levels of post-traumatic stress symptoms. Furthermore, GFD patients had significantly higher anxiety and depression symptom levels. The gut microbiota composition in IBD patients following a VD or GFD was significantly different compared to that of omnivores. Conclusions Although we did not identify a relevant impact of a specific diet on the course of the disease, there was a significant association with lower psychological well-being in VD and GFD patients.

DOI: https://doi.org/10.1177/2050640619841249

Vegetarian or gluten-free diet in patients with IBD – associated with lower psychological well-being and a different gut microbiota but no beneficial effects on the course of the disease

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This work was supported by grants from the Swiss National Science Foundation to the SIBDC [Grant No. 33CS30-148422].

Abstract

Background

Many inflammatory bowel disease patients follow a restrictive diet due to perceived positive effects on their symptoms. We assessed the prevalence of vegetarian (VD) and gluten-free diet (GFD) in IBD patients, the reason for following such a diet and to investigate, whether nutrition has an impact on disease activity and microbiota composition.

Methods

We included 1254 patients from the Swiss Inflammatory Bowel Disease Cohort Study with prospective acquisition of clinical data, psychosocial, disease-related and lifestyle factors between 2006 and 2015. Dietary habits were inquired through a self-report questionnaire. In 92 patients, we analysed intestinal mucosa-associated microbial composition using high throughput sequencing.

Results

Overall 4.1% (n=52) of the patients reported to follow VD and 4.7% (n=54) GFD. No differences regarding disease activity, fistula, hospitalization or surgery rates were observed. Patients on VD or GFD had a significantly higher level of posttraumatic stress symptoms. Furthermore, GFD patients had significantly higher anxiety and depression symptom levels. The gut microbiota composition in IBD patients following a VD or GFD was significantly different compared to omnivores.

Conclusions

Although we did not identify a relevant impact of specific diet on the course of the disease, there was a significant association with lower psychological well-being in VD and GFD patients.

Study highlights:

1. Summary of the established knowledge on this subject

- There exist no guidelines to favor or exclude any dietary habits in IBD
- Many patients with IBD follow specific diets in order to influence their disease

2. What are the significant new findings of this study

- Around 4% of IBD patients are vegetarian and nearly 5% follow a gluten-free diet
- Despite the patient's belief of a favorable disease course, we could not objectify an impact on the disease course
- Gluten-free and vegetarian diet in IBD patients appear to be associated with a lower psychological well-being

Introduction

The incidence and prevalence of inflammatory bowel disease (IBD) has been globally increasing with a more pronounced growth in developing countries[1]. Although the exact pathophysiological mechanisms underlying this increase are unknown, one potential explanation could be the Western diet with high sugar and animal protein and fat intake, especially n-6 polyunsaturated fatty acids, but less consumption of vegetables[2-4]. It is assumed that this "Westernization" of dietary habits can trigger a pro-inflammatory environment[5] in susceptible individuals.

Despite the lack of a general consensus[6-8] or robust evidence[9, 10] on what diet modulate the course of the disease in IBD, a multitude of dietary recommendations have been suggested, such as SCD (specific carbohydrate diet), low FODMAP (fermentable oligosaccharides, disaccharides and monosaccharides) or Palaeolithic diet[11]. This scarce data frequently results in unnecessarily restrictive diets in IBD patients[9].

The prevalence of healthy subjects following a vegetarian diet is around 5% in the USA and in Switzerland[12]. Another important and growing population restricting intake of certain foods are healthy individuals who follow a gluten-free diet (GFD) without having celiac disease. The prevalence of GFD without celiac disease in the USA in 2010 was around 0.5%[13] and reached up to 1.7% in 2014[14] .

Regarding epidemiological data, vegetarian diet may have protective effects on the risk of IBD[15]. However, only a few studies investigated the beneficial or deleterious effects of specific diets on the course of the established disease. Higher intake of meat may increase the risk of a relapse in UC[16] and a semi-vegetarian diet could have a protective effect against relapse of CD[17]. Nevertheless, the data currently is insufficient to recommend any specific diet.

Amongst potential modulators of dietary intake and its effect on intestinal inflammation the intestinal microbiome certainly is a key candidate[18]. Many studies show a microbial dysbiosis in the gut of patients with IBD with lower diversity in their gut microbiota[19, 20]. Although it is still unclear if dysbiosis contributes to the pathogenesis of IBD[21] or rather represents a sequel of the disease itself (the hen and egg question), several studies indicate that the former applies [22].

Changes in IBD patients' diet might promote alterations in the microbial composition that in turn might promote beneficial effects on the course of the disease. Importantly, microbial alterations induced by dietary changes might also induce an adverse effect in terms of development of IBD and adversely impact its course of the disease, as widely suggested by various investigators attributing the increasing incidence of IBD in developing countries to a change in environmental factors, often considered as outcome of 'Westernization'[23].

In this study, we aimed to test for an association of dietary restriction with VD and GFD (two distinctive globally highly prevalent restrictive dietary habits) in SIBDC, a large, prospective and comprehensive cohort study. In addition, we investigate whether mucosa-associated intestinal microbial composition differs between IBD patients based on these daily dietary habits.

Materials and Methods

Study Design and Characteristics

We used prospectively obtained data from the physicians' and patients' baseline and annual follow-up questionnaires from adult patients included in the Swiss IBD Cohort Study (SIBDCS) between 2006 to 2015[24]. In addition, we developed an additional specific questionnaire relating to the patients' diet, which was sent to all patients participating in the SIBDCS (Supplement Questionnaire). The SIBDCS is a nation-wide cohort study enrolling IBD patients in Switzerland since 2006 and is supported by the Swiss National Science Foundation. Data are collected in multiple hospitals, including smaller regional hospitals and large tertiary referral centers, as well as private practices throughout Switzerland. All patients in the SIBDCS who returned the self-reported and the annual follow-up questionnaire were included in the study. The SIBDCS has been approved by the respective ethics committees in Switzerland and the lead ethics committee, Cantonal Ethics Committee of Zurich. The presented study is part of the research plan of the SIBDCS (No. EK-1316, approved on February 5, 2007). Participants were enrolled only after they had provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Outcome Measures

Clinical and disease-related factors were obtained by a physician questionnaire.

Every patient who answered "never" in the questionnaire to the question: "How many times a week do you eat meat" was defined as a vegetarian. As a GFD-patient, we considered all patients who answered "yes" to the question "Are you on a gluten-free diet?"

Independent variables were used to study potential associations with diet (see Supplementary file for variables (1)).

178

179 **Data Analysis**

180 Categorical data were presented as raw numbers and percentages. Differences in categorical
181 variables distribution between two or more groups were assessed using the Chi-square test, or
182 the Fisher's exact test in case of insufficient sample size. Continuous data distribution
183 normality was assessed using normal QQ-plots and is summarized with their median, IQR and
184 range. Differences in continuous distributions between the two groups were assessed using
185 the Mann-Whitney-Wilcoxon Test.

186

187 **Microbiota analysis of biopsies from IBD patients**

188 DNA extraction protocol was carried out for 213 human biopsies of 92 patients within the
189 Swiss IBD cohort using the manufacturer's instructions for All Prep DNA/RNA Mini Kit
190 (Qiagen) kits. Samples were taken alongside the lower gastrointestinal tract (within reach of
191 standard ileo-colonoscopy) starting from ileum and three different locations in the colon and a
192 sample from the rectum as described in the study of Yilmaz et al[25]. There were some samples
193 that were collected from the inflamed part based on the clinician observation however when
194 we analysed for microbiota differences between inflamed and non-inflamed tissue we didn't
195 observed any substantial differences [25].

196 Briefly, 700 µL of Buffer RLT Plus β-mercaptoethanol with a metal bead were added into
197 each sample which were then homogenized using the Retsch Tissue Lyser (Qiagen) at
198 30/frequency for 3 min and followed by 3 min centrifugation at maximum speed (Eppendorf).
199 Supernatants transferred into spin column were centrifuged at 10.000rpm for 1 minute. Then,
200 columns were washed/de-salted using 500 µl of Buffer AW1 and Buffer AW2. 30 µl EB
201 buffer (Qiagen) was used to elute DNA into 1.5 ml microfuge tubes. Afterward, V5/V6 region

of the 16S rRNA genes with the barcoded forward primers was sequenced using IonTorrent PGM platform according to the manufacturer's instructions (ThermoFisher) .

Samples with more than 4000 reads were processed further analysis and initially clustered using QIIME 1.9.1 pipeline. Representative operational taxonomic units (OTUs) were picked after clustering UCLUST with a 97% sequence identity threshold and followed by taxonomy assignment using the Greengenes database. Then, species richness (alpha diversity analysis; Observed OTUs, Simpson and Shannon index) and microbial differences (beta diversity analysis; Bray-Curtis dissimilarities) were calculated in the phyloseq library of R (v3.4). The non-parametric Mann-Whitney U-tests were used to check significant differences in alpha diversity analysis and Adonis (Permanova method on distances; 9999 permutations) were used to assess the statistical significance between groups in beta diversity. A $p < 0.05$ was considered significant. Taxonomy profile associated with clinical metadata was analyzed using multivariate analysis by linear models (MaAsLin) R package and plotted later using ggplot2 library in R. A false discovery rate using Benjamini-Hochberg false discovery rate (FDR; correction) of 0.05, taxa presented at least in 30% of the samples with more than %0.001 relative abundance were set as the cut-off value for significance. Significant taxa were plotted as arcsin-square root transformed microbial relative abundances. To limit preanalytical biases our microbiota analysis between dietary groups are based on mucosa-associated and not faecal samples.

RESULTS

Vegetarian and Gluten-free Diet in the SIBDCS

Of a total of 1,993 patients currently enrolled in the SIBDCS, 1,313 (66%) responded to the dietary questionnaire. 680 questionnaires were incomplete. We included a total of 1,254 patients for the vegetarian and 1,223 for the gluten-free diet analysis. Overall, 4.1% (n=52) of the IBD patients followed a vegetarian diet (VD) and 4.7% (n=57) a gluten-free diet (GFD) with a median duration of 16.1 and 2.8 years, respectively (S-Figure 1 A and B). Most of the gluten-avoiding IBD patients (n=50, 4%) did not have a diagnosis of celiac disease (CeD). A vegan diet was reported by only 0.5% (n=6) of patients. Differences in diet types are seen in table 1 A and 1 B (text in supplementary file (2)).

Amongst GFD-patients (GFDP) we did not observe a gender difference. Differences in GFDP vs. RD are demonstrated in table 2 (text in supplementary file (3)).

Rationale for dietary restriction

In VDP the most frequently reported rational underlying dietary restriction was ‘respect to animals’ (42.3%), while less than one in five patients reported ‘benefits for my IBD’ (17.3%) as the most important rationale. In contrast, the latter rationale (benefits for IBD) was the most frequently reported underlying rationale in GFD patients (40.4%; Figure 1).

Course of IBD

We did not find significant differences in disease activity based on CDAI and MTWAI (S-Figure 2A-D), hospitalization (S-Figure 3), or surgery (S-Figure 4) according to a dietary pattern, neither in GFD nor VD. Likewise, the complication rate was similar in VDP, GFDP

and regular diet patients (RDP) (Figure 2 A). However, in the subgroup of CD (but not UC) patients on VD, we found a significantly lower complication rate (60.5% vs. 42.4%, p=0.039, Figure 2 B and C).

Psychological Variables

VDP had higher scores on the posttraumatic stress diagnostic scale (PDS) (median 7.4 (IQR 3.-11.9) vs. 5.3 (IQR 2.5-9.9); p=0.042) as compared to their counterparts following an RD.

Moreover, VDP had lower mental component levels of the SF-36 with lower levels indicating a lower mental health (median 45.6 (IQR 35.4-50.9) vs. 48.5 (IQR 41.4-53.5); p=0.008; Table 3 A).

GFD was associated with lower scores in the physical and mental component survey (SF-36) (median 48.6 (IQR 42.7-53.6) vs. 51.6 (IQR 45.2-55.1), p=0.026, resp. 42.1(IQR 32.6-48.0) vs. 48.7 (41.8-53.6) p <0.001) and higher anxiety and depression scores (HADS), the higher the score in the HADS-A and HADS-D the greater the level of distress from anxiety or depression, (median 8.6 (IQR 5.3-10.9) vs. 5 (IQR 2.9-7.7) p<0.001, resp. 4.3 (IQR 2.9-6.6) vs. 2.7 (IQR 1-5.3), p<0.001), as well as higher posttraumatic stress diagnostic scale scores (median 8.7 (IQR 4-15) vs. 5 (IQR 2.4-9.3) p<0.001; Table 3 B).

Mucosa-associated microbiota composition in VDP and GFDP versus RDP

Overall, sequences of 213 mucosa-associated samples from 92 patients were available for microbial analysis, including 14 VDP (26 samples) and 12 GFDP (30 samples). Age and BMI, both of which are known microbial composition modifying and thus potential cofounding, factors in these analyses, were relatively evenly distributed across dietary groups (S-Figure 5). Within the majority of meat eating patients (>95% of all SIBDCS patients), we

275 further compared the microbiota of the low vs. high-meat-intake patients (i.e. ≤ 4 vs. >4 days
276 per week) with regards to a potential dose-response.

277 Alpha diversity analysis tended to be higher in GFD CD patients vs. RD CD patients,
278 ($p>0.05$).

279 Within CD patients, the lowest species richness was observed in those patients eating meat >4
280 days per week. In UC patients, the GFD group tended to have the lowest species richness with
281 a trend for the highest species richness in patients eating meat on more than 4 days (S-Figure
282 6).

283 Regarding beta diversity, we identified clustering of samples according to diet type in CD and
284 UC patients (S-Figure 7A and B).

285 Additionally, significant differences in the operational taxonomic units (OTUs) between diet
286 types were seen ($q<0.05$). In CD patients, several representatives of the phyla Bacteroidetes
287 (unassigned OTUs within the genera Bacteroidales, *Bacteroides*, *Prevotella*) and Firmicutes
288 (OTUs within the genera Clostridiales, Faecalibacterium) were significantly correlated with
289 RD patients when compared to the GFD patients (Figure 3). In UC patients, we identified
290 correlation with several OTUs from Firmicutes (unassigned OTUs within Clostridiales and
291 *Ruminococcus* genera) in the meat-eating groups. Within the phylum Bacteroidetes, we
292 observed a positive correlation with *Bacteroides* in the meat eating and *Prevotella* in the GFD
293 group (adj-p value < 0.01) (Figure 3). Analyzing potential differences of specific OTUs
294 between meat-eating and vegetarian UC patients, we found a higher abundance of
295 representative strains from the genera *Bacteroides*, *Faecalibacterium* and *Sutturella* in meat-
296 eating patients and a higher abundance of most representatives from Firmicutes (*Blautia*,
297 *Coprococcus*, *Ruminococcus* and *Dorea*) in the vegetarian group (Figure 4). (Additional
298 results in supplementary file (4)).

299

DISCUSSION

We conducted a cross-sectional analysis in patients from the SIBDCS in order to investigate dietary restrictions, their influence on disease course, and microbiota composition.

In this large investigation on the prevalence of specific diet, a total of 4.1% IBD patients followed a VD. This number of vegetarians is similar to the number in the general population of western countries and analogue to a recently published study from Limdi et al[26] within IBD patients. The main reported reason to follow a vegetarian diet was respect for animals, followed by an expected or perceived benefit on IBD and general health. The latter two motives appear to be considerably more pronounced in GFD eating IBD patients. Our results draw an obvious picture that patients believe their VD or GFD influence their disease positively. However, despite rather strong believes of patients, there is little support for the benefits of a VD or GFD in IBD patients in the existing literature. Due to lack of evidence, neither the ESPEN Guideline for clinical nutrition in IBD nor the ECCO Guidelines support specific dietary habits[6-8].

Overall a total of 4.7% of our IBD patients followed a GFD, most of whom without a diagnosis of CeD. That 4% of IBD patients who follow a GFD without suffering from a CeD in our study doubles the prevalence in the general population, where the rate of GFD is approximately 2%[14]. Our findings are supported by a cross-sectional study of Herfarth et al, in which a high prevalence of GFD (8%) in IBD patients without celiac disease could be seen[27]. Presumably, the higher percentage in IBD patients can be explained by the belief or expectation of a favorable effect on their disease course. This is also indicated by our results regarding the reasons why patients are following a GFD.

In contrast to the beliefs of the patients, our data could not objectify an association of restrictive dietary patterns on the course of IBD. As an exception, however, we identified lower rates of complications in vegetarian CD patients. Although this was only seen in a

subgroup of patients, our findings support the assumption that dietary habits could potentially modulate the course of IBD including a positive overall influence.

Interestingly and in contrast to the results on the clinical course of IBD, psychological variables were significantly different between the dietary patterns. The VD IBD patients had lower mental SF-36 and a higher level of post-traumatic stress symptoms. We hypothesize that these psychological factors and patient expectations are the main driving factor to initiate and continuously follow dietary restriction. The alternative explanation, that refraining from meat would lead to stress and anxiety, seems much less likely. Although our cross-sectional data does not allow drawing conclusions on causality, a study of Michalak et al[28] supports our hypothesis, that psychological factors and expectations affect subsequent dietary restriction.

The number of CeD-free individuals who follow a GFD is continuously increasing[14], but there is no data regarding mood disorders in this subgroup. Our results demonstrate an obvious association of reduced psychological well-being and quality of life with GFD. All psychosocial variables differed significantly between non-GFD and GFD eating patients. Probably gluten-free eating patients have even a stronger tendency towards believing in diet than vegetarian patients and thus try to positively influence their disease by modulating food intake. Our finding further supports this suggestion, that GFD IBD patients in our study are even more prone to attempt alternative medicine. Greater psychological distress is also associated with more somatic symptoms[29] which patients might attribute to IBD prompting them to adjust dietary habits in an attempt to exert control on symptoms

Another important aspect related to dietary restriction in general and meat or gluten specifically is the alteration of microbiota composition. The gut microbiota in vegetarians has been shown to be associated with higher bacterial diversity[30] with a significantly lower counts of pathobionts Enterobacteriaceae [31] and an increase of Prevotella [18, 31], whereas the non-vegetarian diet, especially the western diet, revealed a higher abundance of Bacteroides [18, 21,

[31] and a lower levels of Firmicutes [21]. Furthermore, a GFD in healthy individuals can shift the gut microbiota to fewer and as more healthy considered bacterial strains, including Bifidobacteria and Lactobacillus, with lower counts of E. coli and Enterobacteriacea [32], often considered as rather unhealthy bacteria.

On the other hand, previous studies showed that patients with IBD have a lower diversity in their gut microbiota [19, 20]with an increase in invasive E.coli [33], increase in Enterobacteriaceae family [34] and a reduced proportion of Firmicutes phyla [20].

In our study, the gut microbiota composition in meat-eating IBD patients is significantly different compared to those following a VD or GFD. Our results demonstrate several bacterial changes in regularly meat-eating IBD patients compared to VD or GFD, specifically lower species richness with a dose-response effect in meat-eating CD patients. Interestingly we could see the opposite finding in UC patients with higher species richness in patients with a higher frequency of meat consumption.

Our study has several limitations. First, due to the cross-sectional analysis, we cannot draw any conclusion on cause and effect.

Dietary habits were self-reported, making them potentially unreliable, which is a common limitation in many studies investigating the role of diet in health and disease. Many different food frequency questionnaires exist[35] but due to the specific nature of the questions we created our own questionnaire. However, our dietary questions were distinctively targeted and easily comprehensible, in contrast to many other dietary interrogations aiming to obtain (semi-) quantitative information.

A further weakness relates to the non-available CeD serology. We thus had to rely on the patient reported diagnosis of CeD, which may have led to an over- or underestimation of the IBD patients following a GFD with genuine concomitant CeD. However, most of our IBD patients are well informed regarding their secondary diagnoses.

375 It must be considered that GFD represents a rather recent trend in subjects without CeD ant
376 the duration of GFD in our patient population was considerably shorter as opposed to the
377 duration of VD (S-Figure 1 A and 1 B). Therefore, any conclusions regarding the (long-term)
378 impact of GFD on the course of the disease have to be drawn with caution.

379 In conclusion, our study demonstrates a similar prevalence of VD and a higher percentage of
380 GFD in IBD patients as compared to the general population. We could not observe an
381 association between dietary patterns and the course of IBD with the exception of lower
382 complication rates in VD CD patients. In contrast, VD and GFD were both characterized by
383 adverse psychological scores. Apparently, a significant fraction of IBD patients appears to
384 restrict their diet due to underlying beliefs, expectations or perceptions of beneficial effects on
385 the disease course rather than due to a detectable objective benefit on the course of the
386 disease. Furthermore, we found significant differences in the mucosa-associated gut
387 microbiota composition between VD and GFD IBD patients as opposed to their counterparts
388 not restricting their diet.

389

390 **ACKNOWLEDGEMENTS**

391 The authors wish to thank all the patients for their cooperation in answering the
392 questionnaires.

393

394 **Funding and conflict of interest**

395 There are no conflict of interest for the work under consideration for publication

396 Relevant financial activities outside the submitted work

397 Philipp Schreiner received travel reimbursement from Vifor, Pfizer and UCB and personal fees from
398 Pfizer

399 Bahtiyar Yilmaz reports not to have any potential conflicts of interest

400 Jean-Benoît Rossel reports not to have any potential conflicts of interest

Yannick Franc reports not to have any potential conflicts of interest

Benjamin Misselwitz received travel reimbursement from Novartis; a research grant from MSD and personal fees from Gilead, MSD, Novigenix, Vifor.

Michael Scharl reports not to have any potential conflict of interest

Jones Zeitz received a research grant from Abbvie. Jonas Zeitz has received travel expenses/registration fees for educational events/conferences from Abbvie, Vifor and Almirall.

Pascal Frei reports not to have any potential conflicts of interest

Thomas Greuter received travel reimbursement from Vifor and Falk; a research Grant from Novartis Foundation and personal fees from Sanofi Aventis

Stephan R. Vavricka: received honoraria from Abbvie, MSD, Vifor, UCB, Tillots and research grants from MSD, Abbvie and UCB

Valérie Pittet reports not to have any potential conflicts of interest

Alexander Siebenhüner received consulting honoraria from Amgen, BMS, IPSEN, Lilly, Merck, Pfizer, Sanofi and Servier

Pascal Juillerat reports not to have any potential conflict of interest

Roland von Känel received honoraria from Vifor and Lundbeck Switzerland

Andrew J. Macpherson reports not to have any potential conflicts of interest

Gerhard Rogler reports the he has consulted to Abbot, Abbvie, Augurix, Boehringer, Calypso, FALK, Ferring, Fisher, Genentech, Essex/MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller; Gerhard Rogler has received speaker's honoraria from Astra Zeneca, Abbott, Abbvie, FALK, MSD, Phadia, Tillots, UCB, and Vifor; Gerhard Rogler has received educational grants and research grants from Abbot, Abbvie, Ardeypharm, Augurix, Calypso, Essex/MSD, FALK, Flamentera, Novartis, Roche, Takeda, Tillots, UCB and Zeller.

Luc Biedermann received a research grant from the Swiss National Science Foundation. He received travel reimbursement from Abbvie, MSD and Vifor. Consulting fees from Abbvie, Ferring, MSD, Pfizer, Shire, Takeda, UCB, ThermoFisher, Janssen

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529

530 Table 1 A

531 Characteristics of non-vegetarian and vegetarian diet patients

532

	Not vegetarian	Vegetarian	p-value (chi2 or Mann-Whitney-Wilcoxon)
Number of patients	1202 (95.85%)	52 (4.15%)	
Gender			
Male	582 (48.4%)	14 (26.9%)	**0.002**
Female	620 (51.6%)	38 (73.1%)	
Age at Diagnosis			
Median, q25 – q75, min – max	29.6, 21.7 – 39.6, 3.4 – 81.0	28.1, 20.6 – 35.8, 2.9 – 69.2	0.164
Disease duration			
Median, q25 – q75, min – max	13.2, 7.7 – 21.9, 0.3 – 52.8	13.5, 7.9 – 25.4, 1.3 – 48.7	0.730
Diagnosis			
Crohn	660 (54.9%)	33 (63.5%)	0.225
UC / IC	542 (45.1%)	19 (36.5%)	
Weight (kg)			
Median, q25 – q75, min – max	71, 61 – 82, 37 – 145	63, 55.5 – 72, 47 – 100	**< 0.001**
Weight (stratified by sex; only men)			
Median, q25 – q75,	80, 72 – 87	75.5, 70 – 80	0.175
Min – max	50-145	67 – 90	
Weight (stratified by sex; only women)			
Median, q25 – q75,	63, 56 – 72	60, 52 – 66	**0.038**
Min – max	37 - 135	47 - 100	
Last location of CD			
L1	195 (30.2%)	7 (23.3%)	0.725
L2	239 (37.1%)	12 (40.0%)	(Fisher's exact test)
L3	191 (29.6%)	11 (36.7%)	
L4 only	20 (3.1%)	0 (0%)	
Unknown	*15*	*3*	

Maximal extent of UC Proctitis Left-sided colitis Pancolitis *Unknown*	83 (15.6%) 189 (35.4%) 261 (49.0%) *9*	1 (5.6%) 5 (27.8%) 12 (66.7%) *1*	0.347 (Fisher's exact test)
Previous hospitalization related to IBD No Yes	872 (72.6%) 330 (27.5%)	36 (69.2%) 16 (30.8%)	0.601
Intestinal surgery No Yes	868 (72.2%) 334 (27.8%)	38 (73.1%) 14 (26.9%)	0.892
Surgery for fistula No Yes	1024 (85.2%) 178 (14.8%)	41 (78.8%) 11 (21.2%)	0.211
Complications No Yes	535 (44.5%) 667 (55.5%)	26 (50.0%) 26 (50.0%)	0.436
Fistula or Abscess No Yes	856 (71.2%) 346 (28.8%)	37 (71.2%) 15 (28.8%)	0.992
Stenosis No Yes	879 (73.1%) 323 (26.9%)	38 (73.1%) 14 (26.9%)	0.993
Last measure of CRP (mg/l) Median, q25 – q75, min – max	2.9, 1 – 5.5, 0 – 200	1.15, 1 – 3, 0 – 39	0.069

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535 Therapies & complements

	Not vegetarian	Vegetarian	p-value (chi2 or Mann-Whitney-Wilcoxon)
Therapies (at least once)			
5-ASA	935 (77.8%)	39 (75.0%)	0.637
Antibiotics	470 (39.1%)	21 (40.4%)	0.853
Immuno-modulators	879 (73.1%)	41 (78.9%)	0.361
Biologics	561 (46.7%)	32 (61.5%)	**0.036**
Steroids	990 (82.4%)	46 (88.5%)	0.256
Supplementation therapy (I.6.) No Yes	421 (35.0%) 781 (65.0%)	15 (28.8%) 37 (71.2%)	0.360
In particular: Calcium Iron	314 (26.1%) 114 (9.5%)	23 (44.2%) 12 (23.1%)	**0.004** **0.001**
Alternative medicine (I.7.) No Yes	883 (73.5%) 319 (26.5%)	26 (50.0%) 26 (50.0%)	**< 0.001**

In particular:			
Change in diet and life-style	76 (6.3%)	9 (17.3%)	**0.002**
Shiatsu	21 (1.7%)	3 (5.8%)	0.074 (Fisher)

Table 1B

Ordinal logistical regression (0= no meat, 5= meat consumption every day)

UNIVARIATE ORDINAL LOGISTIC REGRESSIONS	Odds Ratio (95% CI; p-value)
Gender	
Male	1 (ref)
Female	0.494 (0.402 – 0.607; **< 0.001**)
Age at diagnosis (in years)	1.001 (0.994 – 1.009; 0.694)
Age (in years)	0.995 (0.988 – 1.002; 0.167)
Disease duration (in years)	0.988 (0.978 – 0.998; **0.015**)
Diagnosis	
Crohn	1 (ref)
UC / IC	1.062 (0.867 – 1.300; 0.561)
Weight	1.021 (1.014 – 1.028; **< 0.001**)
Last location of CD	
L1 (ileal)	1 (ref)
L2 (colic)	1.153 (0.823 – 1.615; 0.407)
L3 (ileo-colic)	1.004 (0.705 – 1.430; 0.983)
L4 (upper GI only)	1.365 (0.633 – 2.944; 0.428)
Last location of UC	
Proctitis	1 (ref)
Left-sided Colitis	1.307 (0.817 – 2.092; 0.265)
Pancolitis	1.310 (0.836 – 2.054; 0.239)
Previous hospitalization related to IBD	
No	1 (ref)
Yes	0.909 (0.725 – 1.140; 0.410)
Intestinal surgery	
No	1 (ref)
Yes	0.922 (0.735 – 1.156; 0.482)
Surgery for fistula	
No	1 (ref)
Yes	0.880 (0.661 – 1.171; 0.380)
Complications	
No	1 (ref)
Yes	0.950 (0.775 – 1.164; 0.619)
Fistula or Abscess	
No	1 (ref)
Yes	0.890 (0.711 – 1.115; 0.311)
Stenosis	
No	1 (ref)
Yes	0.889 (0.708 – 1.117; 0.313)
Last measure of CRP	1.003 (0.992 – 1.014; 0.601)
Therapies (at least once)	
5-ASA	0.950 (0.743 – 1.215; 0.684)
Antibiotics	0.944 (0.767 – 1.161; 0.584)
Immuno-modulators	1.073 (0.856 – 1.345; 0.542)
Biologics	0.906 (0.740 – 1.109; 0.338)

Steroids	1.080 (0.830 – 1.406; 0.566)
Supplementation therapy	
No	1 (ref)
Yes	0.672 (0.543 – 0.830; **< 0.001**)
In particular:	
Vitamin D	0.726 (0.578 – 0.912; 0.006)
Calcium	0.770 (0.611 – 0.970; 0.026)
Iron	0.636 (0.451 – 0.896; 0.010)
Probiotics	0.610 (0.411 – 0.905; 0.014)
Magnesium	0.650 (0.482 – 0.878; 0.005)
Alternative medicine	
No	1 (ref)
Yes	0.730 (0.582 – 0.917; **0.007**) *
In particular:	
Acupuncture	0.592 (0.376 – 0.931; 0.023)
Bach-flowers therapy	0.314 (0.155 – 0.638; 0.001) *
Anthroposophic medicine	0.196 (0.044 – 0.871; 0.032) *

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542 Table 2

543 Characteristics of non gluten-free and gluten-free diet patients

544

	Non gluten-free	Gluten-free	p-value (chi2 or Mann-Whitney-Wilcoxon)
Number of patients	1166 (95.3%)	57 (4.7%)	
Gender			
Male	560 (48.0%)	21 (36.8%)	0.099
Female	606 (52.0%)	36 (63.2%)	
Age at Diagnosis			
Median, q25 – q75, min – max	29.6, 21.7 – 39.3, 2.9 – 78.1	26.4, 19.5 – 36.8, 10.1 – 81.0	0.085
Disease duration			
Median, q25 – q75, min – max	13.1, 7.7 – 21.9, 0.3 – 52.8	13.7, 7.7 – 21.7, 0.3 – 35.1	0.862
Diagnosis			
Crohn	642 (55.1%)	31 (54.4%)	0.920
UC / IC	524 (44.9%)	26 (45.6%)	
Weight (kg)			
Median, q25 – q75, min – max	71, 60 – 82, 37 – 145	69, 60 – 79, 46 – 100	0.302
Weight (stratified by sex; only men)			
Median, q25 – q75,	79.5, 72 – 87, 50 – 145	76, 69 – 81, 58 – 96	0.109

Min – max **Weight (stratified by sex; only women)** Median, q25 – q75, Min – max	62, 56 – 71, 37 - 135	64.5, 55 – 73.5, 46 - 100	0.477
Last location of CD L1 L2 L3 L4 only *Unknown*	183 (29.3%) 235 (37.7%) 188 (30.1%) 18 (2.9%) *18*	11 (35.5%) 9 (29.0%) 10 (32.3%) 1 (3.2%) *0*	0.679 (Fisher's exact test)
Maximal extent of UC Proctitis Left-sided colitis Pancolitis *Unknown*	84 (16.3%) 180 (35.0%) 250 (48.6%) *10*	3 (11.5%) 8 (30.8%) 15 (57.7%) *0*	0.738 (Fisher's exact test)
Previous hospitalization related to IBD No Yes	850 (72.9%) 316 (27.1%)	41 (71.9%) 16 (28.1%)	0.872
Intestinal surgery No Yes	847 (72.6%) 319 (27.4%)	43 (75.4%) 14 (24.6%)	0.643
Surgery for fistula No Yes	988 (84.7%) 178 (15.3%)	53 (93.0%) 4 (7.0%)	0.124 (Fisher's exact test)
Complications No Yes	522 (44.8%) 644 (55.2%)	26 (45.6%) 31 (54.4%)	0.900
Fistula or Abscess No Yes	828 (71.0%) 338 (29.0%)	46 (80.7%) 11 (19.3%)	0.114
Stenosis No Yes	853 (73.2%) 313 (26.8%)	46 (80.7%) 11 (19.3%)	0.207
Last measure of CRP (mg/l) Median, q25 – q75, min – max	2.8, 1 – 5.1, 0 – 200	2.4, 1 – 8.5, 0.3 – 111	0.803

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547 Therapies & complements

	Not gluten-free	Gluten-free	p-value (chi2 or Mann-Whitney-Wilcoxon)

Therapies (at least once)			
5-ASA	913 (78.3%)	46 (80.7%)	0.667
Antibiotics	456 (39.1%)	17 (29.8%)	0.160
Immuno-modulators	852 (73.1%)	43 (75.4%)	0.694
Biologics	540 (46.3%)	30 (52.6%)	0.350
Steroids	961 (82.4%)	50 (87.7%)	0.302
Supplementation therapy (I.6.)	425 (36.4%)	12 (21.1%)	**0.018**
No	741 (63.6%)	45 (78.9%)	
Yes			
In particular:	305 (26.2%)	22 (38.6%)	**0.038**
Vitamin D	112 (9.6%)	10 (17.5%)	0.051
Iron	69 (5.9%)	11 (19.3%)	**< 0.001**
Probiotics	69 (5.9%)	10 (17.5%)	**< 0.001**
Fish oil / Omega 3			
Alternative medicine (I.7.)			
No	862 (73.9%)	23 (40.4%)	**< 0.001**
Yes	304 (26.1%)	34 (59.6%)	
In particular:			
Homeopathy	68 (5.8%)	10 (17.5%)	**< 0.001**
Change in diet and life-style	67 (5.7%)	17 (29.8%)	**< 0.001**
H15	5 (0.4%)	2 (3.5%)	**0.039** (Fisher)
Anthroposophic medicine	3 (0.3%)	2 (3.5%)	**0.019** (Fisher)
Naturopathy	16 (1.4%)	8 (14.0%)	**< 0.001**
Ayurvedic medicine	5 (0.4%)	2 (3.5%)	**0.039** (Fisher)

548

549

550 Table 3 A

551

552 Psychological scores in non-vegetarian vs. vegetarian patients (for each patient and each
553 score, the mean value during follow-up is computed):

	Not vegetarian	Vegetarian	p-value (Mann-Whitney-Wilcoxon)
Physical Component Summary (SF-36)			
Median, q25 – q75, min – max	51.4, 44.9 – 55.0, 22.2 – 64.3	50.7, 42.0 – 55.7, 28.4 – 64.1	0.511
Mental Component Summary (SF-36)			
Median, q25 – q75, min – max	48.5, 41.4 – 53.5, 12.1 – 66.3	45.6, 35.4 – 50.9, 18.3 – 59.7	**0.008**
Anxiety Score (HADS)			
Median, q25 – q75, min – max	5.2, 3 – 8, 0 – 19.5	6.5, 4 – 9, 1 – 15	0.060
Depression Score (HADS)			
Median, q25 – q75,	2.8, 1 – 5.5,	3.4, 1.3 – 6.2,	0.280

min – max	0 – 18.7	0 – 15.1	
Post-traumatic Stress Diagnostic Scale – Total score Median, q25 – q75, min – max	5.3, 2.5 – 9.9, 0 – 45	7.4, 3 – 11.9, 0.8 – 50.3	**0.042**

554

555

556 Table 3 B

557 Psychological scores in non-gluten free vs. gluten free patients (for each patient and each
558 score, the mean value during follow-up is computed):

559

	Not gluten-free	Gluten-free	p-value (Mann-Whitney-Wilcoxon)
Physical Component Summary (SF-36) Median, q25 – q75, min – max	51.6, 45.2 – 55.1, 22.2 – 64.3	48.6, 42.7 – 53.6, 25.4 – 63.9	**0.026**
Mental Component Summary (SF-36) Median, q25 – q75, min – max	48.7, 41.8 – 53.6, 12.1 – 62.3	42.1, 32.6 – 48.0, 24.1 – 58.4	**< 0.001**
Anxiety Score (HADS) Median, q25 – q75, min – max	5, 2.9 – 7.7, 0 – 19.5	8.6, 5.3 – 10.9, 1.5 – 16	**< 0.001**
Depression Score (HADS) Median, q25 – q75, min – max	2.7, 1 – 5.3, 0 – 18.7	4.3, 2.9 – 6.6, 0.2 – 17.8	**< 0.001**
Post-traumatic Stress Diagnostic Scale – Total score Median, q25 – q75, min – max	5, 2.4 – 9.3, 0 – 45	8.7, 4 – 15, 1 – 35	**< 0.001**

560

561 **Figures legends**

562 Figure 1: Rationale for dietary restriction

563 Figure 2 A: Complication rate in all patients regarding diet pattern

564 Figure 2 B: Complication rate in CD patients regarding diet pattern

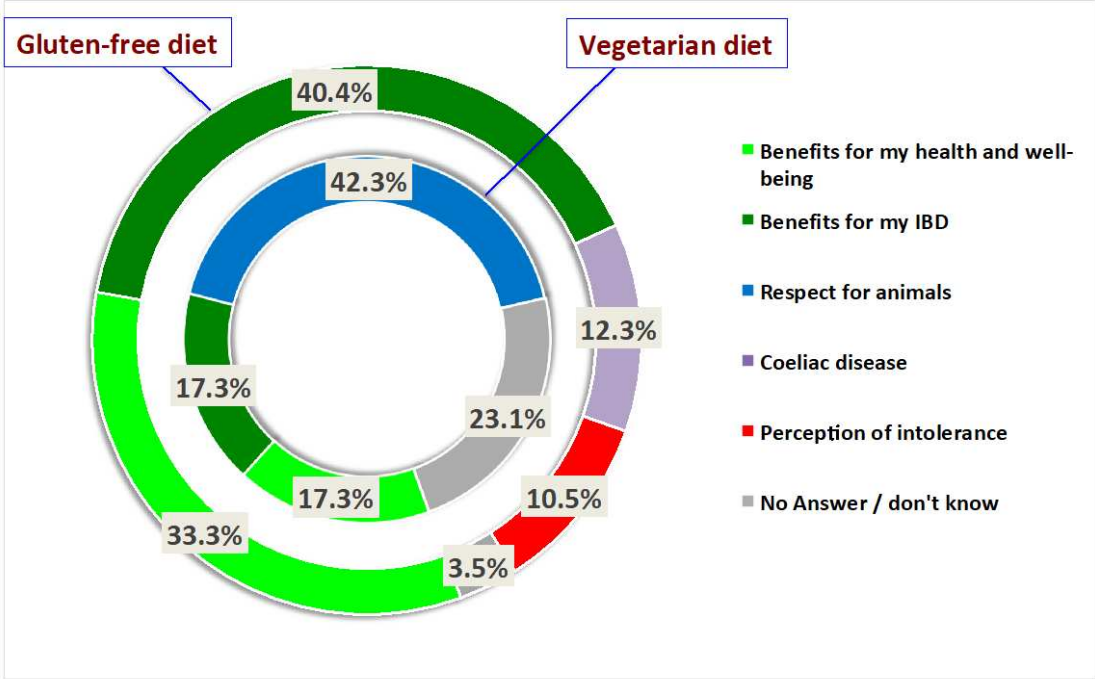
565 Figure 2 C: Complication rate in UC patients regarding diet pattern

566 Figure 3: Significant differences in the abundance of OTUs between Gluten-free vs. regular
567 diet in CD and UC* *All coloured dots without any distribution represent an OTU within the
568 specified genera on the x-axes where no deeper classification is currently availabe

569 Figure 4: Significant differences in the abundance of OTUs between Vegetarian vs. meat-
570 containing Diet in UC

571 Figure 1

572



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586 Figure 2 A

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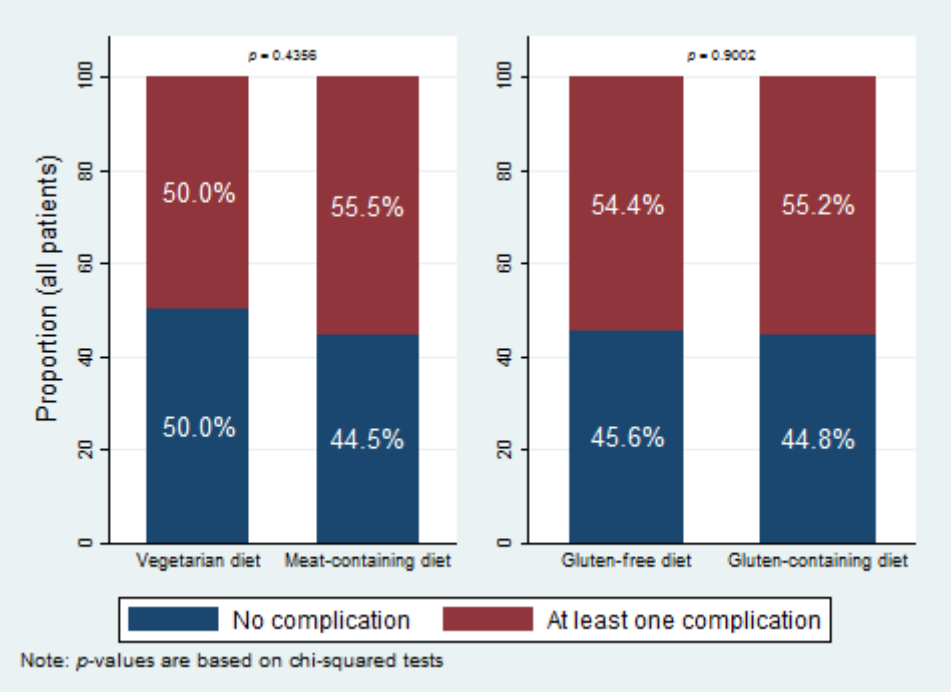

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590 Figure 2 B

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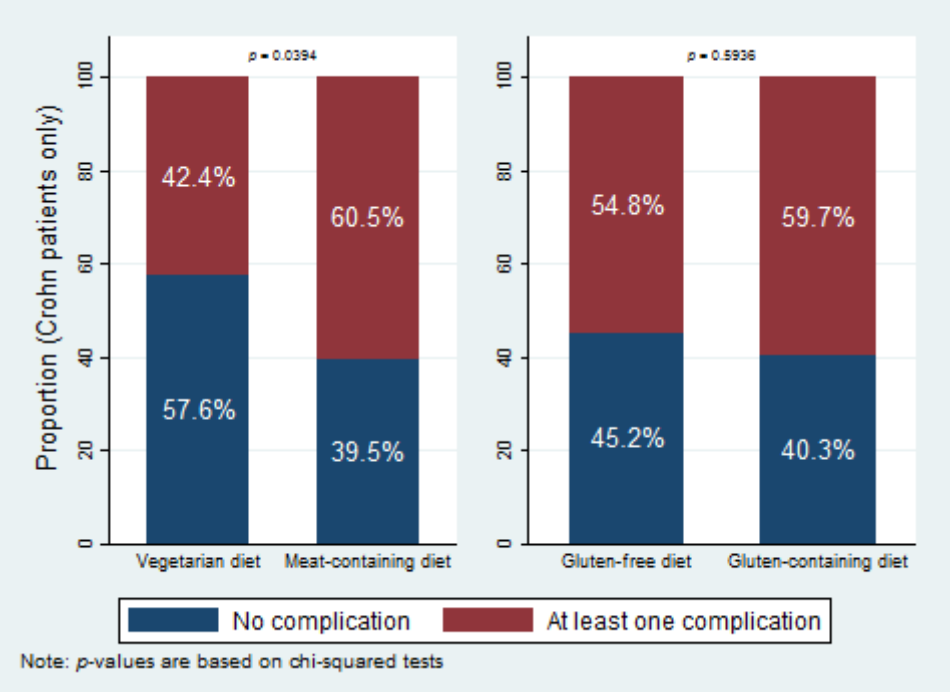
p = 0.0394
p = 0.5936
Proportion (Crohn patients only)
0
20
40
60
80
100
42.4%
57.6%
60.5%
39.5%
54.8%
45.2%
59.7%
40.3%
Vegetarian diet
Meat-containing diet
Gluten-free diet
Gluten-containing diet
No complication
At least one complication
Note: p-values are based on chi-squared tests

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595 Figure 2 C

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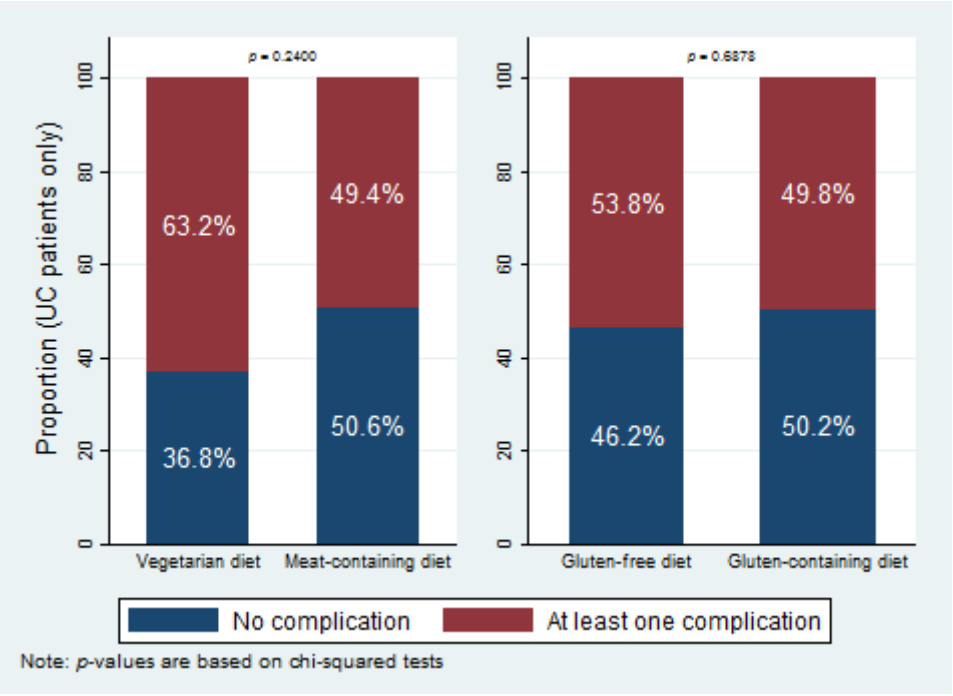

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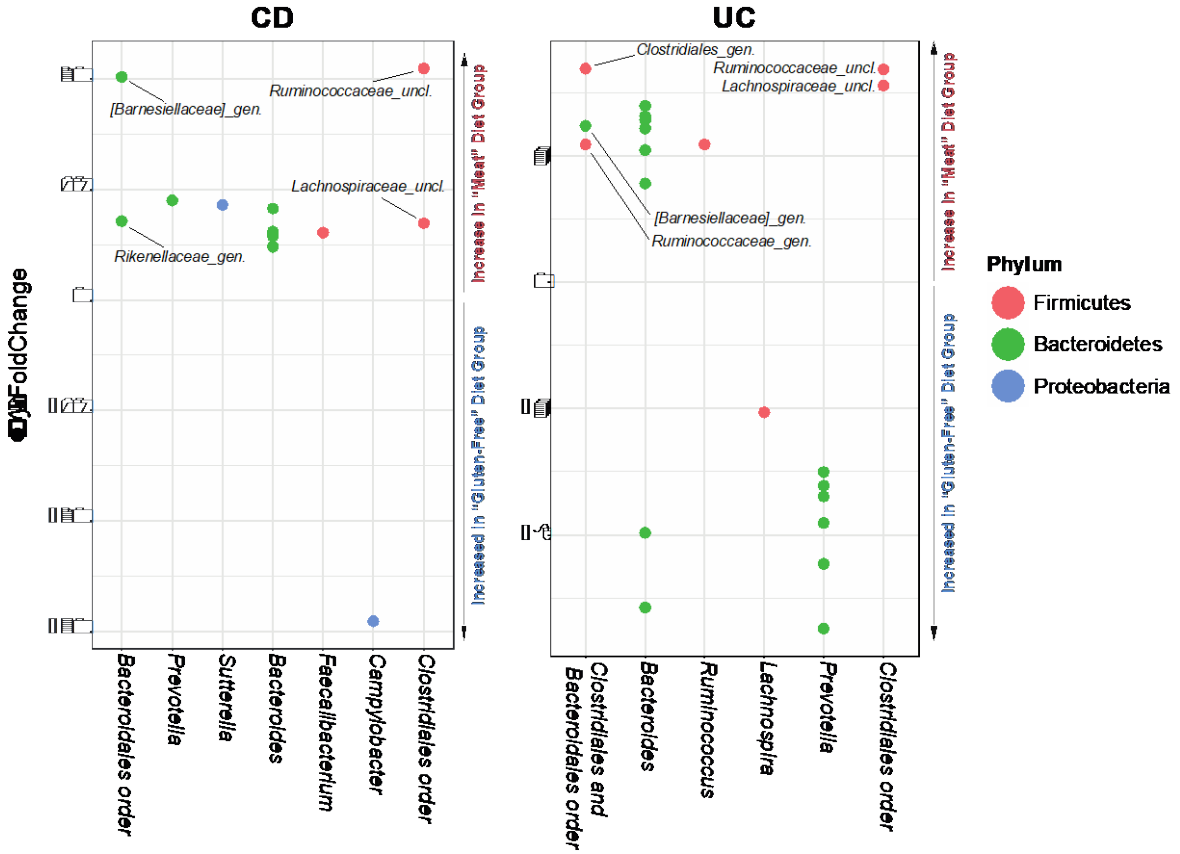
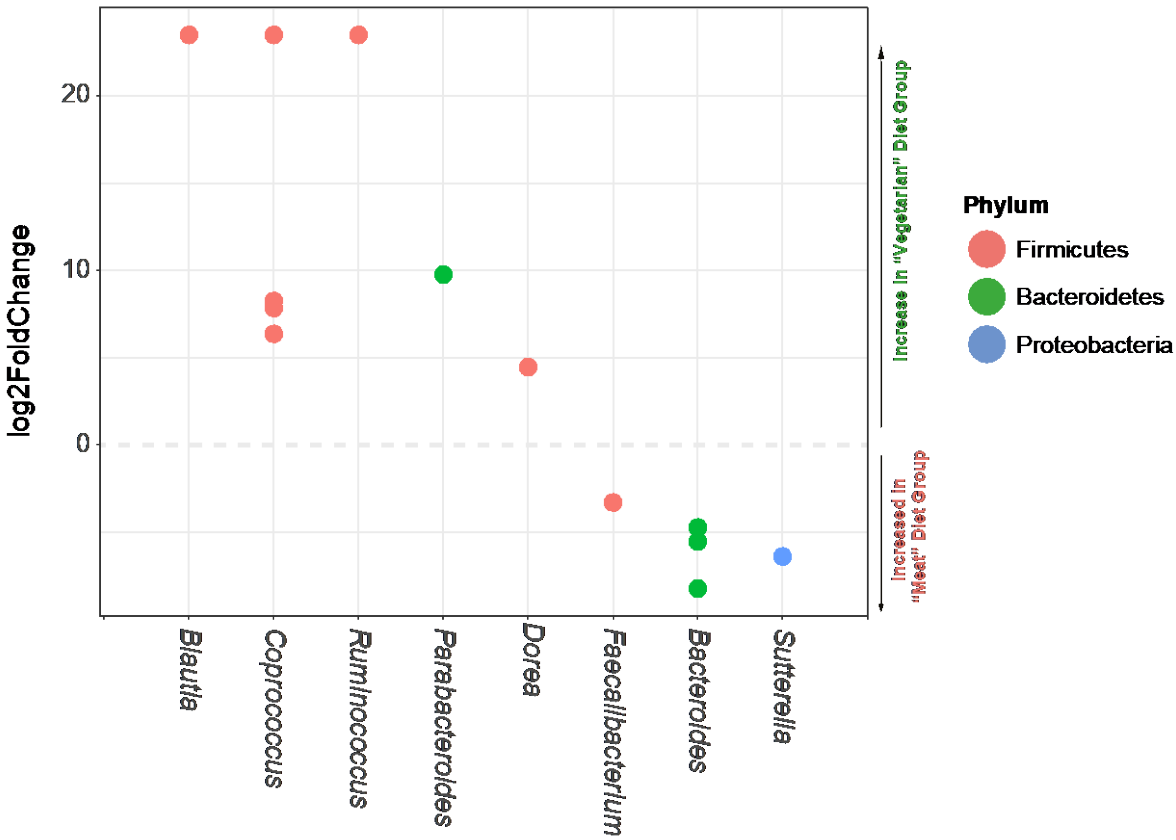
Figure 3


CD
UC
[Barnesiellaceae]_gen.
Ruminococcaceae_uncl.
Lachnospiraceae_uncl.
Rikenellaceae_gen.
Clostridiales_gen.
Ruminococcaceae_uncl.
Lachnospiraceae_uncl.
[Barnesiellaceae]_gen.
Ruminococcaceae_gen.
Increase in "Meat" Diet Group
Increased in "Gluten-Free" Diet Group
Bacteroidales order
Prevotella
Sutterella
Bacteroides
Faecalibacterium
Campylobacter
Clostridiales order
Clostridiales and Bacteroidales order
Bacteroides
Ruminococcus
Lachnospira
Prevotella
Clostridiales order
Phylum
Firmicutes
Bacteroidetes
Proteobacteria

630 Figure 4



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